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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/281,474
Filing Date: March 30, 1999
Appellant(s): RAJOPADHYE ET AL.

Brian J. Hubbard
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/25/06 appealing from the Office action mailed 5/25/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,780,426	Palladino et al	7-1998
6,331,285	Sharma	12-2001

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

Note: Initially (in the office action mailed , the claims were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending application numbers 09/465,300; 09/466,582; 09/599,364; 09/281,209; and 09/948,807. In Appellant's response to the Examiner, it was stated that Appellant would respond to the double patenting rejections once all other rejections were withdrawn. However, since Applicant has responded to the double patenting rejections in the brief and the applications are now US Patent Nos. 6,511,648; 6,558,649; 6,511,649; 6,524,553; and 6,683,163, respectively, the provisional rejections, if applicable to the pending claims, have been converted to non-provisional double patenting rejections.

I. Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of US Patent No. 6,511,648 (application number 09/465,300). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a targeting moiety, chelator, peptide/non-peptide, optionally a metal, and optionally, a linker. The claims differ in that those of the patented invention state that the targeting moiety is a non-peptide whereas the instant invention discloses that the targeting moiety is a peptide.

Appellant asserts that the instant invention differs from that of the patented invention because the patented invention is directed to a non-peptide targeting moiety whereas the instant invention recites a peptide or peptidomimetic targeting moiety.

II. Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,558,649 (application number 09/466,582). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a targeting moiety, chelator, peptide/non-peptide, optionally a metal, and optionally, a linker. The claims differ in that those of the patented invention state that the targeting moiety is a non-peptide whereas the instant invention discloses that the targeting moiety is a peptide.

Appellant asserts that the instant invention differs from that of the patented invention because the patented invention is directed to a non-peptide targeting moiety whereas the instant invention recites a peptide or peptidomimetic targeting moiety.

III. The obviousness-type double patenting over application numbers 09/599,364 (now US Patent No. 6,511,649); 09/281,209 (now US Patent No. 6,524,553); and 09/948,807 (now US Patent No. 6,683,163) is WITHDRAWN because the claims that were directed to the double patenting rejection as set forth in the office action mailed 7/2/02 have been canceled.

IV. Claims 1, 2, 12-15, 17, 19-21, 25, 27, 28, 31-35, 48-50, 52, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palladino et al (US Patent No. 5,780,426) in view of Sharma (US Patent No. 6,331,285).

Palladino et al disclose peptides that may be used to treat diseases involving $\alpha v\beta 3$ receptors. Possible diseases that may be treated include cancer, osteoporosis, restenosis, and angiogenic-based diseases (see entire document, especially, abstract; column 3, lines 33-58). One aspect of Palladino et al is directed to non-RGD (RGD is the peptide sequence Arg-Gly-Asp) peptides that bind to the $\alpha_v\beta_3$ integrin receptor. The peptides are RGD mimics having the sequence Arg-Cys-Asp-Gly-X (RCDG-X) wherein X is any amino acid (column 3, lines 33-58 and columns 3-4, bridging paragraph). In addition, Palladino et al disclose the following (1) the term 'peptide' as defined in their invention means two or more amino acids that are linked together by a peptide bond (column 4, lines 34-35). (2) The peptides may be labelled by incorporating a detectable marker. The marker may be *incorporated* using a radiolabeled amino acid or by the attachment to a polypeptide. Possible labelled that may be used to label the peptide (polypeptide) and *are known in the art include*, using radioisotopes such as 125I, 131I, fluorescent labels, or chemiluminescent agents. Also, *metal binding domains* may be conjugated to the peptides. In some embodiments, labels are attached by *spacer arms* of various lengths to reduce potential stearic hindrance (column 6, lines 37-55). (3) The peptides may be combined with a pharmaceutically acceptable excipient to form a pharmaceutical composition useful for treating disease states or conditions that involve the $\alpha_v\beta_3$ integrin receptor as part of the disease process. In addition, the compounds also form the basis of a diagnostic method or kit for detecting a disease that involves the $\alpha_v\beta_3$ integrin receptor (column 7, lines 22-28; column 12, lines 24-68; and column 13, lines 26-32). (4) In administering the compounds of Palladino et al by a non-

invasive method, there or general methods that may be used to enhance delivery. One may increase the absorption by using a prodrug, chemical modification of the primary structure of the compound, incorporation of the compound into liposomes or other encapsulation material, co-administration with penetration enhancers (i.e., chelators, collagen, enamines, etc) [column 16, lines 42-68]. (5) Palladino et al disclose that In order to determine the level of binding of the peptide to the diseased sample which likely indicates the presence of an angiogenic-based disease state, the peptide is labelled with a detectable label such as a fluorescent or radioactive label. The may be conjugated either directly or indirectly by a single atom or a molecule. *Any label or indicating means may be linked to or incorporated in the protein, polypeptide, or antibody molecule* (columns 20-21, bridging paragraph). The linking of labels (i.e., labelling of polypeptides and proteins) is well known in the art (column 21, lines 13-22).

Sharma et al disclose peptide metalloconstructs that are useful for biological, therapeutic, diagnostic imaging, or radiotherapeutic purposes (see entire document, especially, abstract). The metallopeptide includes a metal ion binding backbone (column 10, lines 59-68). In addition, Sharma et al disclose (a) that the peptides may be RGD peptide mimics (columns 1-13, bridging paragraph; column 13, lines 33-57; column 34, lines 4-13; and column 36, lines 27-37). The peptides may have the metal ion binding backbone complexed with a gamma emitting metal ion, and may be used for imaging thrombosis, cancer, sites of inflammation, or atherosclerotic plaques. In addition, the peptides may have a metal ion binding backbone that is complexed with a non-radioactive metal ion and may be used as a therapeutic agent for myocardial

infarction, thrombosis, restenosis, angiogenesis, bone resorption, or metastatic cancer (column 14, lines 5-13). The peptides may be naturally occurring, produced by chemical synthesis, produced by recombinant DNA technology, produced by biochemical or enzymatic fragmentation of larger molecules, or produced by any other means of producing peptides (column 23, lines 24-58). Various metal ions may be used to label the peptides (column 24, lines 16-47). Various chelators/ligands containing nitrogen, oxygen, and sulfur based coordination atoms may be used to generate a tetradentate peptide construct. The tetradentate structure may be N4, N3S, N2S2, NS3, N2SO, or any similar combination yielding tetradentate coordination utilizing nitrogen, sulfur, and oxygen atoms (column 27, lines 7-49; column 32, lines 26-40; and column 32, lines 57-65). Various spacer groups may be used depending upon the structure desired (columns 27-28, bridging paragraph and column 28, lines 23-45). The design of a biological function domain based upon a desired complexing backbone for complexing metal ions may be performed in at least two different ways. In one approach, the metal ion binding backbone and the biological function domain are merged so that the biologically relevant functional groups are arranged directly on, and are coextensive with, the metal binding domain, and the binding of the metal ion to the metal binding domain fixes the topography of the biological function domain. In another approach, *the biological functional domain is **distinct** from the metal binding backbone*, and the complexation of the metal ion to the metal ion binding backbone (column 30, lines 19-46). Sharma et al disclose various peptides conjugated to a chelating moiety (tetradentate structure) and spacer groups (column 37, lines 35-45; column 39, lines 50-

60; column 45, lines 47-55; column 48, lines 1-10; column 70, lines 40-53; and column 71, lines 29-43)

Appellant assertions are summarized as follows. (A) The combination of references fail to disclose a compound comprising a peptide or peptidomimetic $\alpha_v\beta_3$ receptor targeting moiety bound to a chelator. In particular, Appellant asserts that Palladino et al lacks a chelator. (B) The Sharma et al reference relates to conformationally fixed peptides and metalloconstructs having a metal ion binding backbone and thus, does not disclose a targeting moiety bound to a chelator. (C) The references lack motivation to be combined since while both references are directed to targeting the integrin receptor, their mechanisms appear quite different. Appellant further asserts that Palladino et al is directed to non-RGD targeting moieties and Sharma et al disclose conformationally fixed RGD containing peptides. (D) The linking group of independent claim 1 has a specific formula $(CR^6R^7)_g$-$(W)_h$-$(CR^{6a}R^{7a})_{g'}(Z)_k$-$(W)_{h'}$....' which is not rendered obvious. (E) Claims 2, 12-15, 17, 19-21, 25, 27, 28, 31-35, and 48-50 depend upon independent claim 1 and for the reasons set forth in (D) regarding the specific linker group, the claims are patentably distinct over the prior art of record. (F) Claim 53 recites that the chelator is a diaminedithiol, monoamine-monoamidedithiol, triamide-monothiol, monoamine-diamide-monothiol, diaminedioxime, hydrazine, or cyclic polyaminocarboxylate, or acyclic polyaminocarboxylate which is not obvious over the cited prior art.

(10) Response to Argument

In response to rejections I-V (double patenting rejections) above, the rejections are being maintained on the basis that in each of the patents, the term 'non-peptide' means preferably less than three amide bonds in the backbone core of the targeting moiety or ***preferably less than three amino acids or amino acid mimetics in the targeting moiety*** (see US Patent No. 6,681,163, column 69, lines 64-67; US Patent No. 6,558,649, column 28, lines 14-17; US Patent No. 6,524,553, column 44, lines 62-65; US Patent No. 6,511,649, column 74, lines 25-28; and US Patent No. 6,511,648, column 67, lines 6-9). In the instant invention, see Appellant's disclosure, corresponding to paragraph [0390] in the published US 2002/00015666, the term 'peptide' is defined as a linear compound that ***consists of two or more amino acids*** that are linked by means of a peptide bond. In addition, Appellant discloses that the term 'peptide' also includes compounds containing both peptide and non-peptide components such as pseudopeptide or peptidomimetic residues or other non-amino acid components. Thus, Appellant's use of the term 'peptide' encompasses both peptide and non-peptide targeting moieties.

In response to (A) above, Palladino et al disclose the uses for peptides that include treating diseases such as cancer, osteoporosis, restenosis, and angiogenic-based disease involving $\alpha_v\beta_3$ receptors (see abstract). One embodiment of Palladino et al is directed to non-RGD peptides, thus, the entire reference is not limited to non-RGD peptides, but for what the reference teaches as a whole. Also, Palladino et al disclose that their peptides may be labeled and discloses that a metal binding domains may be

utilized. It should be noted that the phrase 'metal binding domains' is equivalent to 'chelators' in the art (Appellant should review Sharma et al for such teachings). In addition, Palladino et al disclose that the labels are optionally attached by spacer arms of various lengths to reduce potential stearic hindrance. Once again, Appellant's attention is directed to Sharma et al which discloses that the phrase 'spacer' is interchangeable with 'linker' or 'linking group' in the art. Sharma et al is directed to peptides that peptides which may be cyclic RGD mimics, as in Palladino et al, which are complexed with a metal ion binding backbone (chelator) and complexed with a metal. Thus, one of ordinary skill in the art would be motivated to combine the teachings of Palladino et al and Sharma et al since both references are directed to peptides that may be labeled and contain a linking group.

In response to (B) above, while Appellant asserts that the complexes of Sharma et al are conformationally constrained, the pending claims do not exclude conformationally constrained conjugates. In particular, it would be obvious to a skilled practitioner in the art since the conformationally constrained species comprise a targeting moiety (i.e., peptide), a chelator, and a linking group. For example, Appellant's attention is directed to column 39, lines 48-68, of Sharma et al which disclose a metallopeptide comprising a peptide chain, a chelating moiety (N3S containing), and a metal (M). In addition, it should be noted that the peptide chain is linked to the chelating moiety by a spacer group, C(=O) [CO and (C(=O) are equivalent) which is a possible linking group for the linking group of Appellant's independent claim 1, for example, when the variables g, g', k, h', g", h", and g'" are all zero and h = 1 (thus

(W)h is (W) which may be C(=O)). It should also be noted that both Palladino et al and Sharma et al allow for the incorporation of the metal into the backbone of the peptide constructs (see reference disclosure summaries above).

In response to (C) above, while the mechanisms for generating a product may differ, when claims are directed to a product, it is the components of that product upon which patentablility is based. Thus, since both the products of Palladino et al in combination with Palladino et al have the same components as Appellants, it is the components that make up the product that is being examined, not a method of making the product.

In response to (D) and (E) above, the claim discloses that the variables, g, g', k, h', g", h", and g"' may all equal zero. Thus, when h = 1, 'W' = O, S, C(=O), an amino acid, etc. which is illustrated in some of the complexes of Sharma et al. Appellant's attention is directed to column 37, lines 36-45, and column 39, lines 48-60, which disclose a peptide chain linked to a N3S containing chelator by a C(=O) spacer group. In addition, Appellant's attention is directed to the fact that an N3S containing moiety is a triamide-monothiol chelating moiety (see Appellant's claim 53).

In response to (F) above, Appellant's attention is directed to column 27, lines 7-49, in particular, lines 31-45 which disclose that the chelating group may be a N4, N3S (same as Appellant's triamine-monothiol or monoamine-diamide-monothiol combination), N2S2 (same as Appellant's diaminedithiol or monoamine-monoamidedithiol combination), NS3, N2SO, or any similar combination yielding tetradentate coordination utilizing nitrogen, sulfur, and oxygen atoms. Thus, both

Appellant's invention and that of Sharma et al disclose overlapping subject matter. In addition, since Sharma et al disclose that various combinations of nitrogen, sulfur, and oxygen atoms may be utilized to yield a tetradentate structure, a chelating moiety such as diaminedioxime (N2O2 containing) would also be obvious. Also, Appellant's polyaminocarboxylate or acyclic polyaminocarboxylate structure would be obvious since some to the tetradentate chelating moieties contain multiple amino and carboxylate groups (see Sharma et al, column 37, lines 35-45; column 39, lines 51-60; column 45, lines 47-55; column 48, lines 1-10; column 70, lines 40-54; and column 71, lines 29-44)

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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